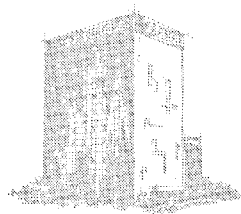


15 SEP 1970

AREA CODE 608
PHONE 262-2177

MEDICAL CENTER



McARDLE LABORATORY FOR CANCER RESEARCH

UNIVERSITY OF WISCONSIN • MADISON, WISCONSIN 53706

September 10, 1970

Dr. Francis Crick
MRC Laboratory of Molecular Biology
Hills Road, Cambridge
CB2 2QH, ENGLAND

Dear Doctor Crick:

Thank you for your letter of August 3. It reached me at Cold Spring Harbor where I was teaching a course in tumor viruses. Since that environment was not conducive to careful consideration of the points you mention, I have delayed answer until my present return to Madison.

In order to keep the discussion clear I shall respond to the points in your letter paragraph by paragraph.

Re: RNA → DNA transfers in uninfected cells. This question is easily susceptible to experimental test, and I hope we shall find such transfer soon. Theoretically, I think that when a cell needs exact long-term storage of information it will use double-stranded DNA, if possible. Single-stranded RNA does not seem to be too stable, for instance there is a very high reversion rate for the mutants of RNA phage and we find a high spontaneous mutation rate for ts-mutants of RSV. The cases of embryonic development and antibody formation require long-term storage plus some cell-to-cell passage and amplification. RNA to DNA transfer might be useful here. Memory formation does not require cell-to-cell passage of the stored information, and so only the stability argument would apply. However, I think that memory formation is a special case of differentiation and so would be based upon some of the mechanisms operative in embryological differentiation, that is RNA to DNA transfer.

Under separate cover, I am sending you copies of several papers. Most of them are on topics not directly related to the RNA to DNA transfer. I would be pleased to receive any suggestions you might have, esp. on the requirement for cell division and on the mechanisms of action of serum.

September 10, 1970

Re: The existence of unknown transfers. The disagreement here is over how versatile living systems are. I find the present complexity of organisms sufficient to make me believe that the complex machinery necessary for the unknown transfers may have evolved. However, the principles used for this machinery might be no different from the machinery used for the general and special transfers. If this latter assumption were true, finding unknown transfers might not ~~be~~ in-of-itself contradict the sequence hypothesis.

Re: The sequence hypothesis. It seems to me two separate questions are involved. One question is what is the primary theorem of present day molecular biologists -- the sequence hypothesis or the central dogma. This question is a historical one, that is what do molecular biologists believe. In my letter of July 27, I was expressing my belief that the sequence hypothesis is more important. Importance is defined here in the sense that demonstration that the sequence hypothesis is not true would have greater consequences for the theoretical basis of molecular biology than would the discovery ~~of~~ a forbidden (unknown) transfer.

The second question is whether or not the sequence hypothesis is true. This is a question about presently existing biological systems. (Sydney Brenner expressed it as whether given the complete DNA sequence of an organism, we could describe the organism). The hesitations I have about the sequence hypothesis are two-fold. First, the DNA sequence must be read in certain standard conditions of temperature, etc. These conditions are not in the DNA sequences. Second, if at one time for some organism the sequence hypothesis was accurate, certain information would always be redundant, that is the information in the DNA sequences for the reading machinery (transcription and translation). This machinery would already be present in the organism. I would guess that there might then be evolutionary pressure for deletion from the DNA sequences of some of the information for the reading machinery. This process would return us to consideration of the central dogma in terms of how this information for the reading machinery would then be transmitted to progeny cells.

Sincerely yours,

Howard M. Temin

Howard M. Temin
Professor of Oncology

HMT:kjp